COMMENTARY

Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT)

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Prostate cancer continues to be a major health threat, especially among African American men. The Selenium and Vitamin E Cancer Prevention Trial (SELECT), which opened on July 25, 2001, was planned to study possible agents for the prevention of prostate cancer in a population of 32 400 men in the United States, including Puerto Rico, and Canada. SELECT is a phase III randomized, placebo-controlled trial of selenium (200 μg/day from *L*-selenomethionine) and/or vitamin E (400 IU/day of *all rac* α-tocopheryl acetate) supplementation for a minimum of 7 years (maximum of 12 years) in non–African American men at least 55 years of age and African American men at least 50 years of age. SELECT is a large, simple trial that conforms as closely as possible with community standards of care. This commentary discusses the design problems the SELECT investigators had to resolve in developing the trial, including the role of prostate cancer screening, the best forms and doses of the study agents, and estimation of the event (prostate cancer) rate of men on the placebo arm. [J Natl Cancer Inst 2005;97:94–102]

Although prostate cancer mortality in the United States has declined in recent years (SEER[1] Cancer Statistics Review 1975–2000), prostate cancer remains the most common visceral malignancy in U.S. men, with 230 110 new cases and 29 900 deaths (the second leading cause of cancer death) estimated for 2004 *(1).* The number of cases is expected to increase to more than 380 000 new cases annually by 2025. The estimated U.S. lifetime risks of prostate cancer development and death are 17.6% and 2.8%, respectively, for Caucasian men and 20.6% and 4.7%, respectively, for African American men *(2).* African American men have the highest such risks in the world. Despite earlier detection with widespread prostate-specific antigen (PSA) screening and advances in prostate cancer surgery and radiation therapy, men treated for localized disease frequently experience morbidity and treatment complications *(3,4).*

The Prostate Cancer Prevention Trial (PCPT), a phase III randomized double-blind, placebo-controlled trial of finasteride for the prevention of prostate cancer, opened in October 1993. Although there is no standard approach for preventing prostate cancer, men who took finasteride (which inhibits 5α-reductase and thus the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate) had a 25% relative reduction (versus placebo) in the 7-year prevalence of prostate cancer *(5).* The overall cancer risk reduction of the PCPT was accompanied by a 1.3% absolute increase in the prevalence of high-grade prostate cancer, which dampened enthusiasm for using finasteride in the preventive setting *(6).*

In April 1998, investigators from the five major U.S. National Cancer Institute (NCI) cooperative groups began planning a prostate cancer prevention trial to follow the PCPT. Although the PCPT was still ongoing, it had closed to accrual in only 3 years (1993–1996) after 18 882 men were randomly assigned to the treatment or placebo arm. The robust PCPT accrual infrastructure involving more than 200 participating sites was still intact, and the next trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), would take advantage of the PCPT and other intergroup sites to accrue more than 35 000 men, making SELECT one of the most ambitious cancer prevention trials ever conceived, and would use two natural agents, selenium and vitamin E. These two agents were chosen mainly

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because of important secondary results of two large completed prevention trials, the Nutritional Prevention of Cancer (NPC) study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study). This commentary describes the development and design of SELECT, which began accrual on July 25, 2001, in the United States, including Puerto Rico, and Canada.

Clinical Design

SELECT is a phase III randomized, placebo-controlled trial of selenium (200 μg/day from *L*-selenomethionine) and/or vitamin E (400 IU/day of *all-rac*-α-tocopheryl acetate) supplementation for a planned minimum of 7 years (maximum of 12 years) for prostate cancer prevention. Eligibility requirements include age of at least 55 years for non–African American men, age of at least 50 years for African American men (age limit lowered because of higher age-adjusted prostate cancer risk among African American men), a serum PSA level of no more than 4 ng/mL, and a digital rectal examination (DRE) not suspicious for prostate cancer. The accrual goal was set at 32 400 men, who will participate from 428 sites throughout the United States, Puerto Rico, and Canada.

SELECT was designed to be a large, simple trial that conforms as closely as possible with community standards of care for men in the SELECT age categories. The primary endpoint of SELECT is the clinical incidence of prostate cancer as determined by routine clinical management and confirmed by central pathology review. During the design of SELECT, substantial consideration was given to the role of PSA and DRE screening in detecting prostate cancer. Although acceptable PSA and DRE results were required at study entry, annual prostate cancer screening with PSA and DRE is not mandatory for SELECT participants. This design decision was made because the benefits of PSA and DRE screening were (and are) still a matter of debate and because community screening standards probably would continue to change over the course of the trial. During annual clinic visits, SELECT participants are encouraged to have PSA and DRE screening completed according to the standard of care at their study sites and their preference.

The decision to use two relatively nontoxic natural agents, selenium and vitamin E, was another important factor in keeping SELECT a large, simple trial. These two agents were chosen for SELECT mainly because of the results of the NPC study and the ATBC Study.

Selenium

A typical U.S. dietary intake of the essential trace element selenium *(7,8)* ranges from 80 to 165 μg/day *(9)*. The recommended dietary allowance for adult North Americans is 55 μg/day, and the safe upper limit of intake is considered to be 400 μg/day *(10)*. The most compelling evidence for testing selenium in SELECT came from the secondary findings of the NPC study, which was conducted in regions of the United States where daily selenium intake is low *(11)*. In this NCI-supported randomized controlled trial, 1312 patients with prior basal or squamous cell skin cancer were randomly assigned to receive 200 μg of elemental selenium per day (in the form of high-selenium yeast) or placebo between 1983 and 1991. Although there was a nonstatistically significant association between selenium intake and an increased incidence of the primary endpoint, nonmelanoma skin cancer, there were statistically significant reductions in the risks of certain secondary cancer endpoints, including a 63% reduction in prostate cancer, 46% in lung cancer, 58% in colorectal cancer, and 53% in all cancer risk. In addition, selenium had no statistically (or clinically) significant toxic effects, although the association with nonmelanoma skin cancer became statistically significant in a recently reported analysis of final NPC blinded results (up to 1996) *(12)*. Data from a prospective U.S. epidemiologic study *(13)*, a large-scale randomized prevention trial in China of a selenium combination that included vitamin E *(14)*, and early preclinical and mechanistic studies *(15–19)* further supported the use of selenium for SELECT. Further supportive data come from a recent epidemiologic study suggesting that selenium may prevent prostate cancer *(20)* and from three recent meta-analyses suggesting that selenium had beneficial effects against lung *(21)*, gastrointestinal *(22)* and colorectal *(23)* cancers.

In December 1998, a panel of nationally recognized selenium experts was consulted for advice on the optimal dose and form of selenium for SELECT. The experts unanimously recommended 200 μg/day as the optimal dose based on preclinical, efficacy, and safety data *(10,11,18)*. Identifying the optimal form of selenium was more complicated. Inorganic selenium compounds, such as selenite, are highly active *(18)* but may not be suitable for long-term use in a prevention trial because of their potential genotoxicity *(24)*. Furthermore, selenite, which is neither absorbed nor retained well, results in substantially lower overall body selenium stores than does the organic compound selenomethionine *(25)*. Although there was considerable interest in using newer selenium compounds, such as monomethylated forms *(26)*, which are metabolized more rapidly to the putative active moiety methylselenol than is selenomethionine, practical and safety considerations (e.g., not commercially available, no investigational new drug certification, and/or insufficient clinical testing data) limited the options to selenomethionine and high-selenium yeast. By a majority vote, the panel experts selected selenomethionine, which was considered to be the major component of high-selenium yeast and thus was associated with the good safety record of selenium yeast in several relatively large long-term clinical trials at daily doses of up to 400 μg of selenium (Marshall JR, personal communication).

The panel of investigators reconsidered the possibility of using the yeast form of selenium because results with yeast would compare directly with the results of the NPC study, which provided the major rationale for selenium in SELECT. Therefore, in July and October 2000, an expanded panel of selenium experts[2] reexamined the decision to use selenomethionine and reevaluated the issue of whether high-selenium yeast may be a preferable source of selenium. However, after reviewing new evidence that indicated substantial batch-to-batch variations in both the presence and relative levels of specific organoselenium compounds in samples of NPC yeast [Uden PC, personal communication and *(27)*] [subsequently supported by new yeast-speciation data *(28)*] and preclinical data involving selenomethionine *(18)* [subsequently confirmed and extended by other investigators *(29–34)*], the panel reaffirmed the original decision to use selenomethionine at 200 μg/day.

Vitamin E (α-Tocopherol)

Vitamin E has eight different forms—α-, β-, γ-, and δ-tocopherols and α-, β-, γ- and δ-tocotrienols—with varying

activity and mechanism profiles relevant to cancer prevention *(35,36).* The U.S. average daily intake of vitamin E is approximately 10 mg for men and 7 mg for women of naturally occurring, or *all-rac*-α-tocopherol—levels that are substantially lower than the 15 mg recommended by the Institute of Medicine Food and Nutrition Board for both men and women *(10).* Although all forms of vitamin E are absorbed, only certain stereoisomers of α-tocopherol are maintained in human plasma and tissues. Therefore, only α-tocopherol currently is considered to contribute to the recommended daily allowance for vitamin E. There are eight stereoisomers of α-tocopherol. The synthetic α-tocopherol *all rac*-α-tocopheryl acetate has all eight stereoisomers and is the most common vitamin E found in supplements.

The strongest evidence in support of including vitamin E in SELECT as a potential prostate cancer preventive agent came from a secondary analysis of the large randomized, controlled ATBC Study. This trial, conducted in Finland by the National Public Health Institute of Finland and the U.S. NCI, was designed to determine whether α-tocopherol in the form of *all rac*-α-tocopheryl acetate (50 mg daily) and/or β-carotene (20 mg daily) would reduce the risk of lung cancer among 29 133 male smokers aged 50–69 years *(37).* Although the incidence of lung cancer paradoxically increased among men receiving β-carotene, the incidence of new prostate cancer cases and prostate cancer mortality statistically significantly decreased by 32% and 41%, respectively, among the 14 564 men receiving vitamin E (versus men not receiving vitamin E) *(38).* Additional substantial preclinical *(35,39)* and epidemiologic *(40,41)* data suggesting that vitamin E may inhibit carcinogenesis, including in the prostate, further supported the inclusion of vitamin E in SELECT. Indeed, recent data also suggest that vitamin E can disrupt androgen-receptor signaling in prostate cancer cells *(42,43),* thus suggesting a mechanism for the potential anticarcinogenic effects of this agent in the prostate.

The ATBC Study led to the choice of α-tocopherol for SELECT, but a debate arose over the best dose and formulation of α-tocopherol to use. It was suggested that 50 mg of *all rac*-α-tocopheryl acetate (the selection of this formulation is discussed below) would provide a direct comparison with the ATBC Study and would be a favorable dose with respect to γ-tocopherol levels, which can be displaced by α-tocopherol, in SELECT participants; however, this low dose was rejected ultimately for several reasons. First, a further analysis of the α-tocopheryl intervention in the ATBC Study suggested that men with higher baseline, and thus total, α-tocopherol levels had a greater reduction in prostate cancer incidence *(44)* and a reduced risk of lung cancer *(45),* compared with men having lower baseline (and thus total) levels. Second, plasma γ-tocopherol levels are decreased in persons given supplementments of as little as 30 mg/day of α-tocopherol *(46),* and there is conflicting evidence on whether a further reduction in γ-tocopherol levels is seen with higher levels of α-tocopherol supplementation *(47,48).* Because there is a lack of strong scientific evidence supporting the hypothesis that a decrease in γ-tocopherol harms human health, the influence of α-tocopherol on γ-tocopherol levels did not appear to be a valid reason to limit the α-tocopherol dose in SELECT (γ-tocopherol is further discussed below). Third, there were clinical data supporting higher doses of α-tocopherol for potential benefits such as reductions in Alzheimer's disease and age-related macular degeneration *(49–51).* Therefore, it was decided that vitamin E as *all rac*-α-tocopheryl acetate would be used in SELECT at a daily dose of 400 IU (equivalent to 400 mg), which is found in vitamin supplements and was believed to be potentially more protective (than lower doses) against prostate cancer *(44).*

Decades of research have supported the safety of vitamin E for human use *(10)* (National Institutes of Health Office of Dietary Supplements, Vitamin E, http://ods.od.nih.gov/factsheets/vitamine.asp; revised October 2004). All forms of vitamin E at the same dose are considered to have similar toxicity because all forms are absorbed, although not all are preferentially incorporated into plasma and tissues. The tolerable upper limit of intake for any form of supplemental vitamin E in adults is 1000 mg/day, and the lethal dose to kill 50% of test animals (LD_{50}) for α-tocopheryl acetate is greater than 2000 mg/kg for rats, mice, and rabbits. Controlled clinical trials of α-tocopherol, including trials of doses of 1000 or more IU/day, had indicated no statistically significant adverse effects, with the exception of an increased risk of hemorrhagic stroke among the subgroup of male smokers with uncontrolled hypertension in the ATBC Study *(52)* and an adverse effect on retinitis pigmentosum among patients with this disease *(53).* Therefore, for reasons associated with potential toxicity, SELECT exclusion criteria included uncontrolled hypertension, use of anticoagulant medications (with the exception of cardioprotective doses of aspirin), and the presence of retinitis pigmentosum. A few months after SELECT had completed its accrual, however, the report of a meta-analysis of several randomized controlled trials suggested that high-dose vitamin E (up to 2000 IU/day) may increase mortality from all causes *(54).* This new information on vitamin E was submitted to the SELECT Data and Safety Monitoring Committee [as were the above-mentioned nonmelanoma skin cancer findings on selenium reported in 2003 *(12)*] to assist in the Committee's continuing vigilance for any adverse effects, including mortality or illness, of vitamin E, selenium, or the two agents combined. Another recent meta-analysis, which raised concerns about increased overall mortality in association with antioxidants in general *(22),* reported no findings of harm associated with either selenium or vitamin E alone or in combination with each other.

Compared with the selenium formulation considerations, the decision to use vitamin E in the form of *all rac*-α-tocopheryl acetate was made relatively easily, given both its activity in the ATBC Study and its absorption and metabolism in humans. Supplements made from naturally occurring *RRR*-α-tocopherol that have approximately twice the biologic activity of synthetic forms *(35,36)* exist, but because there have been no controlled trials of this form in disease prevention, *RRR*-α-tocopherol was excluded as a potential choice for SELECT. Alternative esters (e.g., succinate), which are very active in vitro *(55),* were also excluded from SELECT because they are efficiently hydrolyzed before absorption and have no biologic activity with oral administration in humans.

Recent epidemiologic data have suggested that γ-tocopherol may surpass α-tocopherol in the ability to prevent prostate cancer and challenged the choice of α-tocopherol *(56).* However, the absence of prospective data on γ-tocopherol testing in humans for safety or activity weighed against seriously considering γ-tocopherol for SELECT. Furthermore, experimental data indicated that γ-tocopherol has a greater antiplatelet effect than does α-tocopherol, suggesting a greater potential for the vitamin E–related risk of hemorrhagic stroke *(57).* Mechanistic consid-

erations and other biochemical evidence also supported the choice of α-tocopherol over γ-tocopherol *(35,36,57,58).* Moreover, both serum and prostate tissue concentrations of α-tocopherol are approximately 10-fold greater than are those of γ-tocopherol because the hepatic α-tocopherol transfer protein has a high relative affinity for the *RR* forms of α-tocopherol *(59).* More recent studies of serum tocopherols and prostate cancer risk show a decreased risk associated with α-tocopherol and a less-to-no decreased risk associated with γ-tocopherol *(60,61).*

Selenium Plus Vitamin E

The combination of selenium and vitamin E had been evaluated clinically in only one prior cancer prevention trial, the General Population Trial (GPT) of the Nutrition Intervention Trials in Linxian, China *(14).* The GPT found that the combination of selenium at 50 μg/day, α-tocopherol at 30 mg/day, and β-carotene at 15 mg/day reduced total mortality, total cancer mortality, and gastric cancer incidence and mortality with no adverse effects. Although the GPT combination included β-carotene, recent data suggest that α-tocopherol and selenium were the active components *(62).* The direct relevance of the GPT data to SELECT were limited, however, because the GPT study population was generally undernourished (versus the anticipated SELECT population of well-nourished men) and few incident prostate cancers occurred. In addition, data from nonprostate cancer animal models had shown that the combination of selenium plus vitamin E was beneficial in suppressing carcinogenesis and without adverse interactions *(63,64).* For example, the combination reduced the level of oxidative DNA damage more than did either agent alone, particularly in animals at the margins of nutritional deficiency for either agent *(63,64).* Recent in vitro data in prostate cancer cells also indicate that selenium and vitamin E interact favorably *(65,66).* Therefore, selenomethionine at 200 μg/day, *all rac*-α-tocopheryl acetate at 400 IU/day, and the combination of these agents at these doses were chosen for SELECT.

Statistical Design and Study Implementation

Statistical Design

A sample size of 32 400 men for SELECT and the associated power calculations were based on a number of underlying assumptions and estimates, the most difficult of which were the assumptions leading to the estimate of the incidence of prostate cancer among men in the placebo group. Prostate cancer rates had declined sharply between 1995 and 1997 because of the subsiding effects of PSA screening in producing lead-time bias and subsequently increased rates of prostate cancer. However, during the design of SELECT, the latest official nationwide Surveillance, Epidemiology and End Results (SEER) data were from 1991–1995, during which time the PSA-associated lead-time bias was in effect. Therefore, the SELECT study population would be drawn from a screened population, which would have a lower incidence of prostate cancer than that estimated by the national SEER data.

These considerations led to conservative event-rate estimates. We estimated that the incidence rate of prostate cancer in the first 3 years of the trial would be similar to the rate from the PCPT. For years 4 to 12 of SELECT, we estimated events based on regional rates from the Seattle/Puget Sound SEER data for all races combined, which (in contrast to national SEER data) covered the years 1994 through 1997 and were stratified by age. These data indicated that the peak prostate cancer incidence in the Seattle/Puget Sound region occurred in 1991 and that age-specific incidences had remained constant between 1994 and 1997. We anticipated that the incidence of prostate cancer in the SELECT population would be higher than the relevant SEER age-related incidence primarily because most SELECT men probably would receive annual screening with DRE and PSA (versus men in the SEER database) and that the SELECT population probably would include a substantial percentage of intensively recruited African American men.

We estimated a 25% treatment effect for either selenium or vitamin E. This estimate is conservative vis-à-vis the secondary analyses of the NPC study and ATBC Study, indicating that selenium and vitamin E were associated with reductions of greater than 60% and greater than 30%, respectively, in prostate cancer incidence during the interventions.

SELECT assumed that 10% of the men randomly assigned to placebo would take an active study supplement (i.e., drop-in). Although prospective clinical data supported this assumption, some investigators thought that the percentage was too low and thus detrimental to the study power/sample size. Our drop-in assumption was justified, however, by data from the ongoing Heart Outcomes Prevention Evaluation (HOPE), a randomized, controlled cardiovascular disease prevention trial showing 10%–15% drop-ins to vitamin E.

SELECT will be analyzed as a four-arm study, with primary analyses consisting of five pairwise comparisons of prostate cancer incidence, in association with: vitamin E versus placebo, selenium versus placebo, vitamin E plus selenium (combination) versus placebo, combination versus vitamin E, and combination versus selenium. This analysis plan avoids the need to make the assumptions about potential interactions of vitamin E and selenium that would have to be made with a more traditional 2×2 factorial analysis (of the main effects). Such an analysis would pool across study arms to make only two comparisons: vitamin E (vitamin E plus placebo and vitamin E plus selenium) versus non–vitamin E (selenium plus placebo and placebo plus placebo) and a similar comparison for selenium versus non-selenium. SELECT was designed to have adequate power to test the difference between the arms hypothesized to have the lowest event rates (Table 1). This design results in 89% statistical power for comparing an effective single supplement versus the combination, 96% for a single supplement versus placebo, and greater than 99% for the combination versus placebo. The high power of SELECT provides protection against possible errors in estimates of incidence, drop-in, and other assumptions, including rates of death and loss to follow-up.

SELECT also will assess several prespecified secondary endpoints—prostate cancer survival and lung, colorectal, and overall cancer incidence and survival. The power to detect a 25% decrease in the overall cancer incidence is 90%, but for the other secondary analyses is lower because their rates in the SELECT population are anticipated to be low. Secondary endpoints are being collected primarily because of their potential importance for generating hypotheses for other trials. To monitor the safety of vitamin E with regard to the risk of hemorrhagic stroke, SELECT also implemented the collection of serious cardiovascular event data.

Table 1. Power calculations of SELECT primary endpoints*

Comparison	Underlying hazard-incidence	% relative risk reduction	% power
Single agent vs. placebo	PCPT/SEER	25	96
Single agent vs. placebo	PCPT/SEER	22	90
Combination vs. placebo	PCPT/SEER	44	>99
Combination vs. effective single agent†	PCPT/SEER × 0.75	25	89

*PCPT = Prostate Cancer Prevention Trial; SEER = Surveillance, Epidemiology and End Results.
†An effective single agent would reduce the underlying hazard-incidence rate by 25%.

Interim analyses are planned for 5, 7, 9, 10, and 11 years after the first participant is randomly assigned. The expected percentages of the anticipated total number of prostate cancer events at these analyses is 14%, 35%, 61%, 74%, and 88%, respectively. For each interim analysis, testing of the null hypotheses will be done at a one-sided level of 0.0005. In addition, the alternative hypothesis of a 25% reduction in prostate cancer incidence will be tested at a one-sided level of 0.0005 by using an extension of the log-rank test that allows for testing a relative risk not equal to 1. An interim analysis with $P<.0005$ would suggest extreme positive results or a clear lack of benefit and would trigger the consideration of stopping the trial.

PCPT data *(67)* indicated that a formal placebo run-in period would be unnecessary to assure compliance, and so such a procedure was omitted from SELECT. There was a formal prerandomization period (minimum of 28 and maximum of 90 days), however, for potential participants to decide whether they would agree to stop disallowed supplements of selenium or vitamin E throughout the study and to demonstrate—by returning afterward for random assignment—their willingness to adhere to the trial.

We were concerned that the completion of the PCPT could lead to nonadherence or drop-outs if finasteride was found to prevent prostate cancer. If the use of finasteride was sufficiently widespread, it would have the potential of decreasing the estimated event rates in all study arms and thus decreasing the power of the study. However, results of the PCPT published in 2003 indicated that, although finasteride reduced the overall risk of prostate cancer, its use was also associated with an increase in the diagnosis *(68)* of high-grade disease *(5,6).* Because of these mixed PCPT findings, finasteride is not currently considered a general prostate cancer prevention agent, thus minimizing a finasteride-related adherence or drop-out problem for SELECT.

The statistical assumptions for SELECT (e.g., event rates in the study arms and overall drop-in rates) were based largely on data from the large-scale randomized, controlled ATBC and NPC studies and from HOPE and PCPT, data that are generally stronger than those supporting prior phase III cancer prevention trials. The SELECT statisticians and Data Safety and Monitoring Committee will continually reassess these assumptions as the trial unfolds.

Implementation

Implementation of SELECT involved many important considerations. SELECT is managed primarily through the SELECT Workbench, a secure Web site that is administered by the SELECT Statistical Center and accessible to study site staff and investigators only. The Workbench contains the SELECT protocol, a study manual with procedures and guidelines to augment the protocol, and a variety of materials to assist sites in performing all activities associated with randomization, participant follow-up, and study administration. A public SELECT Web site, accessible to study participants, was initially implemented to promote interest in the study; it is now used to keep SELECT in the public's eye and to help in retaining participants.

Study site staff members receive training on SELECT procedures at semiannual meetings conducted by the SELECT coordinating research base, the Southwest Oncology Group (SWOG). This training consists of presentations, small group breakout sessions on specialized topics of interest, and poster sessions. SELECT protocol forms were designed to optimize their processing and management via an electronic document management system featuring both Web-based and fax transmissions of data from the study sites. In general, forms completed by the participant are faxed to the Statistical Center, and those completed by the study site are submitted electronically via the SELECT Workbench. A system of edit checks implemented at the time of Web-based data transmission from the study sites and during review at the Statistical Center contributes to the overall quality control review. Data are stored in an Oracle database; electronic documents and digitized images of forms are archived in a disk storage system. The SWOG Operations Office conducts Study Site Quality Assurance Audits at least once every 3 years.

Study site staff can access a variety of reports via the SELECT Workbench. These reports provide information such as identification of time requirements for individual participant follow-up activities, study supplement assignment information for reconciling pharmacy inventory, Institutional Performance Review information for all study centers, interactive query reports for data clarification, and updated accrual statistics and form submission status for each study site. These reports ensure that all study sites have access to the same type of current information.

If any participant is diagnosed with prostate cancer, then the study site is required to submit representative hematoxylin and eosin–stained slides for confirmation of prostate cancer to the central SELECT Pathology Review Laboratory housed in the Prostate Diagnostic Laboratory at the University of Colorado. In addition, the study site is required to submit pathology material for any participant with the diagnosis of high-grade prostatic intraepithelial neoplasia (grades 2 or 3) or a suspicious/atypical finding. Submission of additional pathology materials for future studies are encouraged via appropriate compensation to the site. Uniform Gleason grading and detailed histopathologic and biomarker studies will be performed on the submitted materials. Ten sites will participate in a substudy in which additional pathology materials are submitted from all prostate procedures,

including negative biopsy specimens to serve as negative controls in future studies. Information regarding other cancers, documented by the study site, will be supported by local pathology reports and other clinical records. Data on toxicities that are possibly, probably, or definitely related to the study supplements are being collected every 6 months during the participant interview on a study site–completed form. There are also guidelines for the immediate reporting of Grade 3–5 unexpected and Grade 4–5 expected reactions that are possibly, probably, or definitely related to the study supplement(s).

Other Important Design Considerations

Recruitment

Recruiting and enrolling 32 400 healthy men who are willing to take two study pills every day for 7 to 12 years was a substantial challenge. One of the earliest steps to meet this challenge was the formation of the Recruitment and Adherence Committee and the Minority and Medically Underserved Subcommittee, consisting of members from the NCI cooperative groups and other diverse organizations involved in the trial. These committees oversaw recruitment in the 428 study sites located throughout the United States, including all 50 states, Puerto Rico, and the District of Columbia, and in five Canadian provinces (Alberta, British Columbia, Nova Scotia, Ontario, and Quebec). A strong emphasis was placed on identifying clinical sites that could recruit high numbers of minorities, particularly African Americans. This effort resulted in the early productive involvement of leaders from organizations such as the National Association for the Advancement of Colored People, the National Medical Association, and the National Black Leadership Initiative on Cancer and in selecting for participation in many SELECT sites involved with the Women's Health Initiative, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Department of Veterans Affairs Cooperative Studies Program—each with potential for recruiting high numbers of African American men. SELECT accrual was completed and closed on June 24, 2004, 2 years ahead of the planned 5-year schedule. The unexpectedly rapid overall enrollment was largely the result of extraordinary coverage in the national and local media of the launch of the trial, which generated 10% of the total accrual within 4 months of activation, and to selecting effective recruitment sites (based largely on demonstrated performance in previous large-scale cancer prevention trials), which maintained higher than expected monthly accrual rates.

SELECT minority recruitment goals were 24% all minorities, 20% African Americans, 3% Hispanics, and 1% Asians. We also worked to recruit medically underserved participants, regardless of ethnic background. The emphasis on African American recruitment was based on the increased disease burden within this group. SELECT's number and percentage of African Americans (Table 2) are the highest for any cancer prevention trial conducted in the United States. This success was the result of several factors, including the risk-based lowering of the minimum age requirement of African American men to 50 years (versus 55 years for all other men) (which resulted in 33% of all enrolling black participants being younger than 55 years), African American enrollment in Veterans Affairs (19%) and Minority-Based Community Clinical Oncology Program (16%) sites, and Minority Recruitment Enhancement Grants (MREGs) to sites with high minority-recruitment potential (which resulted in higher accrual of blacks in MREG than in non-MREG sites). Nevertheless, SELECT's African American accrual fell short of the 20% goal, reaching 15% (Table 2). This shortfall was due primarily to the early closure of accrual because of the unexpectedly rapid overall accrual rate. Certain highly effective

Table 2. Recruitment and characteristics of all participants randomly assigned in SELECT*

Total accrual = 35 534 men	% of total	Total accrual = 35 534 men	% of total
Recruitment base		Baseline PSA, ng/mL	
SWOG	32	0.1–1.0	48
ECOG	14	1.1–2.0	31
CALGB	10	2.1–3.0	14
RTOG	2	3.1–4.0	7
NCCTG	8	Race/ethnicity	
CUOG	6	White	78
VA†	12	African American	15
WHI‡	9	Hispanic	5
ALLHAT	4	Asian/Pacific Islander	1
None	5	Family history of prostate cancer	
Age, y		Yes	17
Median	62.4	No	83
Minimum	50.0	Highest level of education completed	
Maximum	93.1	Grade school	3
Age group, y		High school (all or some) or GED	21
50–54	5	Vocational school	5
55–64	58	College (all or some)	40
65–74	31	Graduate school (all or some)	31
75+	6		

*SELECT = Selenium and Vitamin E Cancer Prevention Trial; SWOG = Southwest Oncology Group; ECOG = Eastern Cooperative Oncology Group; CALGB = Cancer and Leukemia Group B; RTOG = Radiation Therapy Oncology Group; NCCTG = North Central Cancer Treatment Group; CUOG = Canadian Urologic Oncology Group; VA = Department of Veterans Affairs; WHI = Women's Health Initiative; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial of the National Heart, Lung, and Blood Institute; PSA = prostate-specific antigen; GED = General Educational Development.

†Some VA sites overlap with other bases, accounting for the apparent excess of accrual in this list; VA sites include sites of the Department of Veterans Affairs Cooperative Studies Program.

‡WHI sites recruited to become SELECT sites were still following women randomly assigned from 1993 through 1998 to receive either estrogen plus progestin or placebo in the WHI (N = 16 608).

minority recruitment methods, such as MREGs, were not implemented until accrual was underway, and the early accrual closure did not provide enough time to achieve the African American accrual goal with these methods.

Multivitamin Considerations

We anticipated that many SELECT participants would take multivitamins, which often contain vitamin E and selenium. To avoid inadvertent drop-ins or nonadherence, via the intake of non–study-related vitamin E and/or selenium from multivitamin capsules, we provided SELECT participants with free bottles of a specially formulated multivitamin containing neither study agent. However, this multivitamin contained vitamin D, and its use raised the concern that the SELECT statistical power could be reduced by fewer event rates resulting from the potential preventive effects of vitamin D. Nonmalignant human prostate cells express 1-α-hydroxylase, the enzyme that converts 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D *(69,70),* which can inhibit the proliferation and invasiveness of prostate cancer cells *(71).* Nevertheless, the decision was made to include vitamin D in the multivitamin formulation because it is essential to bone health in SELECT-aged (i.e., aged at least 50 years) men. We originally formulated the SELECT multivitamin to contain half of the 400 IU adequate intake dose *(72)* for vitamin D (in the form of vitamin D_3) for men aged 51–69 years, which was judged healthful but unlikely to confound or weaken the primary endpoint findings of the trial, but this decision proved to be controversial among SELECT investigators and institutional review boards. Notwithstanding the preclinical activity *(70,71),* no studies have reported associations between prostate cancer risk and either vitamin D intake (up to 800+ IU/day) or multivitamin use *(73,74)* [e.g., possibly because of confounding factors such as sunlight exposure, which recently was shown to be associated with prostate cancer risk *(75)*]. Therefore, we determined that the level of vitamin D in multivitamins was unlikely to affect the overall event rate in SELECT and reformulated the multivitamin to contain the full adequate intake dose for vitamin D (400 IU of vitamin D_3).

Ancillary Studies

SELECT will examine a number of important translational ancillary study endpoints involving molecular epidemiology, cellular and molecular biology of carcinogenesis, nutrition-related factors, other medicines, other age-related diseases, and health-related quality of life. The SELECT design included a prospectively collected biorepository of white blood cells (including viable lymphocytes), red blood cells, plasma, and other tissue samples (e.g., toenails) for ancillary correlative studies and has been reported in detail elsewhere *(76,77).*

Budgetary Compromises

Several compromises were made to keep the SELECT budget within feasible limits. For example, participants are followed up twice rather than four times per year, as was done during the PCPT. Limitations were imposed on collecting additional data, e.g., clinical information such as other medications, and biospecimens for research.

Conclusions

Multidisciplinary investigators from the five major U.S. cooperative and other groups worked closely together in solving the complex problems of the SELECT design. Their success is reflected by the rapid completion of SELECT accrual (Table 2) 2 years ahead of the planned 5-year schedule. Although SELECT did not meet the goal of accruing 20% African American men, it has improved substantially on the unsatisfactory record of the PCPT and many other cancer prevention trials in accruing African American and other minority and medically underserved participants.

The major issues regarding the selenium formulation and the vitamin E dose, form, and formulation were complex, which may seem surprising in a trial of readily available, over-the-counter agents. The numerous natural and synthetic forms of nutritional compounds, their wide range of supportive evidence (preclinical, epidemiologic and clinical) of varying strengths, and vast amounts of good and bad reporting on these compounds in the popular press (which can influence recruitment and adherence) are a few of the many reasons that designing a definitive cancer prevention trial of nutrients is far from a straightforward simple process.

New findings of adverse and beneficial effects of the study agents *(12,20–23,31,54,78–86),* such as from four recently reported meta-analyses *(21–23,54),* continue to influence SELECT, with regard to participation and adherence if not specifically with regard to design. SELECT is challenged by an environment of evolving standards for prostate cancer screening and early detection. For example, recent findings that prostate cancer risk is higher at lower PSA levels than previously thought *(87)* could alter screening standards and patterns in the community and, therefore, prostate cancer rates in the trial. These and other new data result in a constant process of amending the SELECT design and procedures to assure the validity of its outcomes and safety of its participants.

With more than 200 000 new cases of prostate cancer diagnosed annually in the United States alone, this disease remains a major public health burden. The value of selenium and/or α-tocopherol in reducing this burden will be determined by the men participating in and adhering to the rigorously designed SELECT.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

[2]Seven experts on selenium sat on the second panel: Howard Ganther, Gerald Combs, Orville Levander, Blossom Patterson, Clement Ip, Peter Uden, and Raymond Burk, the first four of whom also sat on the earlier expert panel convened in 1998.

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